meta-Selective C–H Arylation of Phenols via Regiodiversion of Electrophilic Aromatic Substitution

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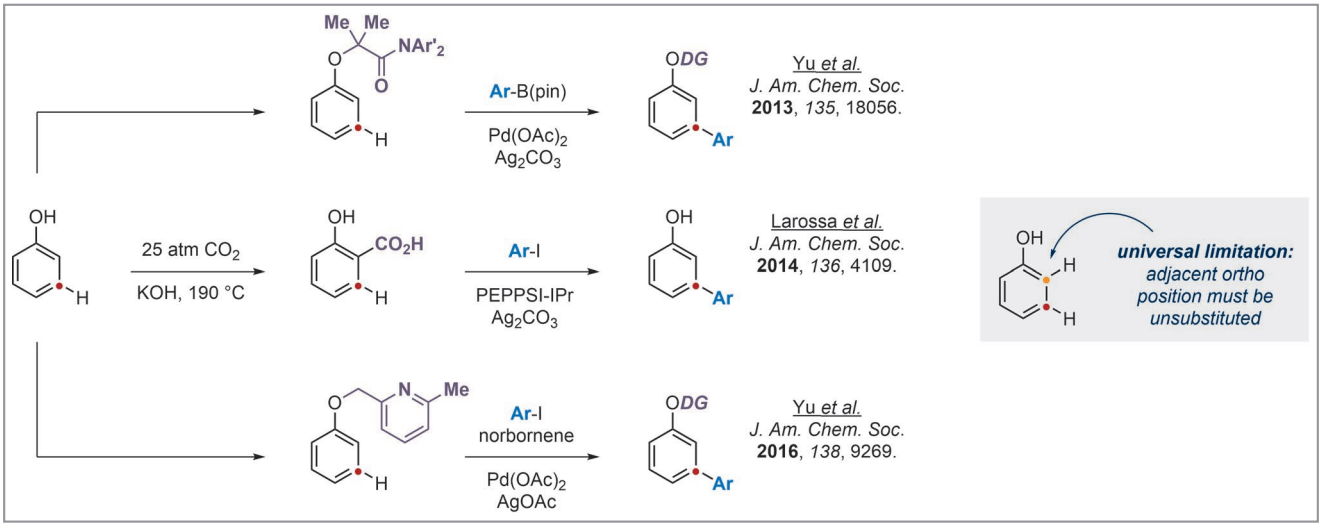
The *meta*-selective C–H arylation of phenols is an enduring challenge in organic synthesis (*Chem. Rev.* **2022**, *122*, 5682). Not only is the *meta* position deactivated towards electrophilic substitution – the most common reaction manifold for phenols – but it is also beyond the reach of most directing groups that could be appended to the phenolic oxygen. Although this challenge has attracted several pioneering solutions based on Pd-catalyzed C–H functionalization (Scheme 1), these methods do not tolerate an existing *ortho* substituent on the phenol. As such, phenols featuring contiguous substitution patterns (e.g., 2,3-disubstitution) remain severely underrepresented in chemical libraries (*J. Med. Chem.* **2020**, *63*, 13389).

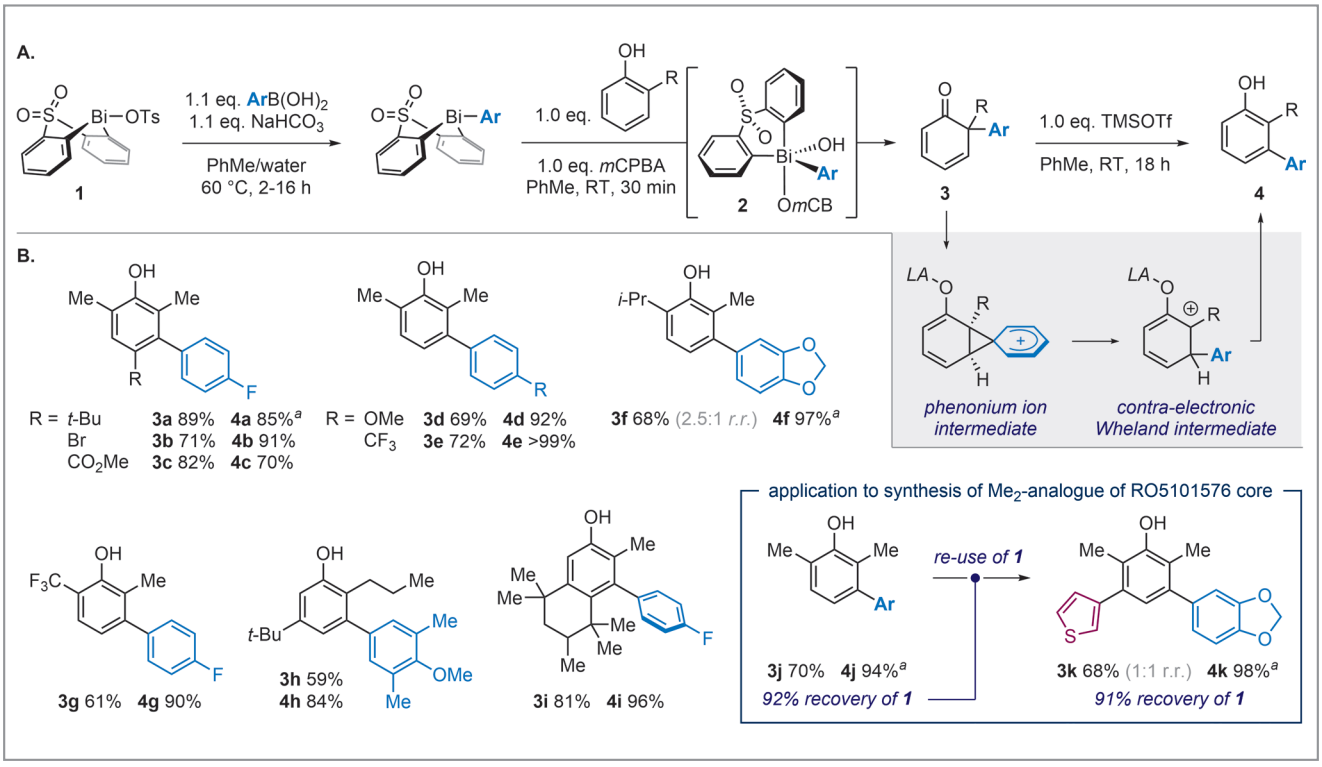
Dr Liam Ball and his team at University of Nottingham (UK) recognized that they could potentially address this limitation using a fundamentally different reaction manifold: Bi(V)-mediated electrophilic arylation. The group recently reported a convenient and highly *ortho*-selective Bi(V)-mediated arylation (*Nat. Chem.* **2020**, *12*, 260). Dr Ball explained: "This appears to proceed *via* an S_EAr-like mechanism in which the "Ar^+" electrophile is added to the π-system of the phenol *prior* to cleavage of the C–H bond. This is obviously very different to Pd-catalyzed C–H functionalizations that typically involve concerted metalation deprotonation, where the new C–C bond is formed *after* the C–H bond is cleaved." The group hypothesized that the electrophilic manifold could be applied equally to the arylation of *ortho*-substituted phenols to give a dienone intermediate which would be prevented from spontaneously rearomatizing. "If we could then induce a dienone–phenol rearrangement," Dr Ball continued, "1,2-aryl migration would effectively form a new Wheland-type intermediate *meta* to the phenolic OH, but without having to actually achieve the initial substitution at this least reactive position."

This hypothesis was borne out in practice (Scheme 2). Following the group's established protocols, telescoped B-to-Bi transmetallation and oxidation converted the bench-stable Bi(III) 'universal precursor' **1** into the active Bi(V) arylating agent **2**, which was then reacted with an *ortho*-substituted phenol to give the corresponding dienone **3** (Scheme 2A). Treatment of isolated dienone **3** with a Lewis acid promoted the 1,2-arylation/rearomatization sequence, giving *meta*-arylated phenol **4**.

Aaron Senior, the first-named author on the paper and a PhD candidate at the time of the work, led reaction development and exploration of substrate scope (Scheme 2B). "The



Scheme 1 Precedent for the *meta*-selective C–H arylation of phenols



Scheme 2 Selected examples of *meta*-selective C–H arylation via a Bi(V)-mediated arylation/rearrangement sequence. [a] 1,2-Aryl migration performed using $Bi(OTf)_3$ (20 mol%) and NEt_3 (20 mol%) in place of TMSOTf, 60 °C.

process was shown to be compatible with electronically and sterically diverse phenols (**4a–c**) and boronic acids (**4d,e**)," said Dr. Senior. He continued: "Notably, migration occurred smoothly to place the aryl moiety adjacent to even very bulky *tert*-alkyl substituents (*e.g.*, **4a**); in this case, buffered conditions were required to prevent dealkylation via a *retro*-Friedel–Crafts reaction. Non-symmetrical phenols were arylated at the more sterically accessible and more electron-rich *ortho* position (**4f,g**), consistent with the electrophilic nature of the arylation. Substrates with a single *ortho* substituent were also tolerated (**4h,i**), with excellent regioselectivity observed for sterically biased substrates."

A key feature of the methodology is that the bismacyclic reagent 1 can be recovered and re-used. Dr Ball recalled: "Aaron identified the core of RO5101576 as an ideal showcase for the recyclability of the bismacycle [see Scheme 2B, inset]: the same batch of reagent was used in two sequential arylations, with only about 15% of the bismuth being lost over the whole process."

The group used kinetic isotope effects and linear free energy relationships to shed light on the mechanism of the key aryl-migration step. The data were consistent with migration occurring via a phenonium intermediate, in which significant positive charge accumulates on the migrating substituent.

"By combining two known concepts – Bi(V)-mediated arylation and the dienone–phenol rearrangement – we were able to provide a novel solution to a longstanding synthetic challenge," said Dr Ball. He concluded: "The methodology provides a valuable complement to better established approaches to *meta*-selective arylation based on Pd catalysis, and we are excited to continue exploring the opportunities it offers."

About the authors

Dr. A. Senior

Aaron Senior completed his undergraduate degree at the University of Nottingham (UK) in 2017, which included a Masters project on drug discovery with Dr. Andrew Nortcliffe. He subsequently enrolled in Nottingham's EPSRC Centre of Doctoral Training in Sustainable Chemistry (UK), completing a training year before joining the Ball group in 2018. Aaron completed his PhD in 2022, and is now a Senior Scientist at Pharmaron in Hoddesdon, UK.

Dr. K. Ruffell

Katie Ruffell graduated with an MSc in chemistry from the University of Nottingham (UK) in 2018, following a placement year at GSK Stevenage (UK) and final-year research with Prof. Chris Moody. Her PhD in the Ball group was sponsored by Syngenta, and included a placement at their Jealott's Hill site in 2020. Katie defended her thesis in 2022, and is currently a Senior Scientist at Charles River Laboratories in Saffron Walden, UK.

Dr. L. Ball

Liam Ball obtained his undergraduate degree from the University of Bristol, UK. Following doctoral studies with Dr Chris Russell and Prof. Guy Lloyd-Jones FRS at the University of Bristol (UK, 2009–2013), he moved to the University of Edinburgh, UK, as a postdoctoral researcher with Prof. Guy Lloyd-Jones FRS (2014–2015). In 2015, Liam was appointed Assistant Professor of Organic Chemistry at the University of Nottingham (UK), where he is now an Associate Professor and UKRI Future Leaders Fellow. His research centers on exploiting mechanistic insight in the design and development of new synthetic methods.

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